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10/540,522	12/20/2007	Masaru Uemura	052767	5365

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ART UNIT	**PAPER NUMBER**
1651	

NOTIFICATION DATE	DELIVERY MODE
11/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentmail@whda.com

Office Action Summary	Application No.	Applicant(s)	
	10/540,522	UEMURA ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *11-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 19-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/24/05, 5/9/06, 1/3/07, 5/7/10.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 9/10/10 to the claims have been entered. Claims 28-30 have been added. Claims 1-30 remain pending in the current application.

Election/Restrictions

Applicant's election without traverse of Group 1, claims 1-10 and 19-30, in the reply filed on 9/10/10 is acknowledged. Claims 11-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to show a fixed support for cultivating container (2) in Figure 1 as described in the specification. See page 9, lines 9-10. Currently, the cultivating container in Figure 1 is not attached to the inner frame (7) by any means. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate

changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 19-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a method comprising two steps: in step (a), the differentiation of multipotent stem cells is suppressed by some unspecified means, and in step (b), the differentiation of multipotent stem cells is induced. However, the claim does not clearly set forth a clear relationship between these steps, especially since there are two cultivating containers. It is not clear whether the claims include a method in which one sample of cells is cultivated in a first container at the same time a second sample is cultured in a separate second container. If applicant intends for steps (a) and (b) to be sequential, this point could be clarified by adding the words "and then" to the end of step (a). Furthermore, the limitations "while suppressing differentiation" and "inducing

differentiation" are wholly functional and do not indicate any particular method step that would give rise to these ends. Finally, step (b) requires "applying a force," but since the Earth inherently exerts gravitational force on every object, and every object inherently exerts gravitational force on every other object, it is not clear whether this "applying" requires an active step or whether the inherent gravitational forces exerted by objects would suffice. Clarification is required.

Claim 19, the other independent claim, is drawn to a composition containing two "means," which may be an attempt to use a "means" clause to recite a claim element as a means for performing a specified function. However, since no clear function is specified for the "means," it is impossible to determine the equivalents of the element, as required by 35 U.S.C. 112, sixth paragraph. See *Ex parte Klumb*, 159 USPQ 694 (Bd. App. 1967). The examiner notes that the specification also does not define the "means." The metes and bounds of the claim cannot be evaluated. Clarification is required.

A single claim that claims both a product or apparatus and the method steps of using said product or apparatus is indefinite under 35 U.S.C. § 112, second paragraph. In *Ex parte Lyell*, 17 USPQ2d 1548 (Bd. Pat. App. & Inter. 1990), a claim directed to an automatic transmission workstand and the method steps of using it was held to be ambiguous and properly rejected under 35 U.S.C. § 112, second paragraph. See M.P.E.P. § 2173.05(p). In this case, claims 19-17 and 29 appear to be drawn to an apparatus and method steps of using the same. For example, claim 19 refers to "applying a force" and "promot[ing] the differentiation" of cells. Claims 20 and 21 refer to

the application of force and rotation. Claim 26 requires a step of mixing. Claim 29 refers to a method and adds 5 specific active steps. Clarification is required. The claims must be amended such that they clearly recite only one category of invention under 35 U.S.C. § 101.

Because claims 2-10 and 20-30 depend variously from indefinite claims 1 and 19 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claims 2, 3, 20, and 21 require “dispersing a direction of application of gravitation . . . three-dimensionally,” which is extremely confusing language. It is not clear how a “direction” can be “dispersed.” It is not clear how the "application” of “gravitation” can be completely “directed.” The world exists in three dimensions (actually, in four – length, width, depth, and time). Clarification is required.

Claims 3 and 21 require “carrying out an n-axis rotation (n is an integer of 2 or more),” which is confusing because it is not clear whether the matter within the parentheses is necessarily part of the claims. Furthermore, it is not clear whether the “dispersion of the direction of application of the gravitation” is an inherent effect of this n-axis rotation or whether it requires some particular type of rotation to occur. Clarification is required.

Claims 4 and 22 require that one of two axes be "a direction of the gravitation," but it is not clear whether the gravitation refers to that of the Earth, that of the objects surrounding the container, or that applied in claim 2. Clarification is required.

Claims 5 and 23 refer to "the gravitation," which finds no basis in parent claims 1 and 19. Clarification is required.

Claims 6 and 24 require that the force be greater than "a magnitude of the gravitation," which is confusing for two reasons. First, it is not clear whether the force must be greater than some unnamed order of magnitude relative to the gravitation. Second, it is not clear which gravitation is being compared. Clarification is required.

Claims 7 and 25 require the force exerted to be a resultant force of some gravitation and some centrifugal force, which is confusing because it is not clear how this centrifugal force is generated. Claims 7 and 25 do not depend from any claim that requires rotation. Clarification is required.

Claims 8 and 26 refer to "a differentiation inducing agent," which is a wholly functional limitation that does not clearly include or exclude any particular compound. The claims do not limit the end point of the differentiation. While describing a product in terms of its function is not itself improper (see *In re Swinehart*, 439 F.2d 210, 169USPQ 226 (CCPA 1971)), claims directed to a product should be distinguished from the prior art product in terms of structure rather than function; this point was recently revisited. "When a claim limitation is defined in purely functional terms, the task of determining whether that limitation is sufficiently definite is a difficult one that is highly dependent on context (e.g., the disclosure in the specification and the knowledge of a person of ordinary skill in the relevant art area). We note that the patent drafter is in the best position to resolve the ambiguity in the patent claims, and it is highly desirable that patent examiners demand that applicants do so in appropriate circumstances so that

the patent can be amended during prosecution rather than attempting to resolve the ambiguity in litigation." *Halliburton Energy Services, Inc. v. M-I LLC*, 85 USPQ2d 1654, 1663 (Fed. Cir. 2008). Such ambiguity could be resolved in a few ways, for example by providing a quantitative metric for the property, or a formula for calculating the claimed functional property along with examples and counterexamples of products with that property. While functional claiming is authorized by 35 U.S.C. § 112, sixth paragraph, that statute was enacted specifically to preclude overly broad claims that effectively purport to cover any and all limitations, so long as they perform the required functions. Specifically, claims that are ambiguous as to boundaries for functional limitations may be indefinite and do not distinguish the claimed product over the prior art. Clarification is required.

Claims 9, 10, and 27 refers to "a same apparatus" for "cultivating" and the "cultivating step," which is confusing. Applicant should clarify whether these steps are carried out sequentially within the same apparatus or whether they may be carried out, sequentially or separately, in two apparatuses identical in structure. Clarification is required.

Claim 29 refers to "the method of cultivating stem cells according to claim 25" and then recites 5 active steps, which is improper because claim 25 is drawn to an apparatus, not a method. Clarification is required. Each claim must include only one of the categories permitted under 35 U.S.C. § 101.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-8, 19-21, and 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Plett et al. (2001, *In Vitro Cell and Developmental Biology – Animal* 37: 73-78; reference 1 on 5/7/10 IDS). Claim 1 is interpreted as being drawn to any method in which stem cells are first proliferated and then differentiated. Claim 19 is drawn to any apparatus that carries out such a method.

Plett teaches isolating CD34+ hematopoietic stem cells (HSCs) from bone marrow and culturing them in a rotating wall vessel (RWV), which simulates microgravity. (Page 74, column 1.) Plett teaches culturing the cells in media, then supplementing the media every 48 hours with growth and differentiation factors. (Page 74, column 1.) Plett teaches removing HSCs from the RWV and culturing them in methylcellulose media to differentiate them into various hematopoietic colonies; therefore, as required by claim 1, the HSCs' differentiation is suppressed to at least some degree. (Page 74, column 2.) Because Plett's experiments were conducted on Earth, the methylcellulose cultures are subject to the force of gravity.

Claims 19-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Yugen Kaisha ECT (2002, JP 2002-45173; reference 2 on 6/24/05 IDS).

Yugen Kaisha ECT teaches a culture apparatus containing a culture vessel inside an envelope that rotates around both an X-axis and a Y-axis. (See translation of detailed description, supplied by applicants, at paragraphs 24, 25, and 27; see also Figures 2 and 3.) Yugen Kaisha ECT teaches that the simultaneous two-axis rotation gives rise to a resultant force that provides circulation of culture medium. (Translation of detailed description, paragraph 27; Figure 4.).

Claims 19-27 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Uemura et al. (2003, U.S. Patent Application Publication 2003/0041800; reference 1 on 5/9/06 IDS). Uemura is the work of "another" because the inventive entity of that reference is not identical to the inventive entity of the instant application.

Uemura teaches an apparatus comprising a cultivation vessel attached to a "three-dimensional klinostat," a machine that rotates a sample around plural axes and provides a microgravity environment for cells within the vessel. (Paragraphs 4, 7-9, 12, 22, 29-31, 48, and Figure 1, e.g.). Uemura teaches including a "cultivation promotion factor" in the medium. (Paragraph 47.) Uemura's example contains an inner and outer frame with the cultivating container attached to the inner frame, wherein the inner and outer frames rotate around axes orthogonal to each other. (Figure 1.)

The applied reference has one inventor in common with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 19-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plett et al. (2001, *In Vitro Cell and Developmental Biology – Animal* 37: 73-78; reference 1 on 5/7/10 IDS) taken in view of Goodwin et al. (1996, U.S. Patent

5,496,722; reference A), Matthews et al. (1998, U.S. Patent 5,851,984; reference B), and Yugen Kaisha ECT (2002, JP 2002-45173; reference 2 on 6/24/05 IDS).

Plett teaches isolating CD34+ hematopoietic stem cells (HSCs) from bone marrow and culturing them in a rotating wall vessel (RWV), which simulates microgravity. (Page 74, column 1.) Plett teaches culturing the cells in media, then supplementing the media every 48 hours with growth and differentiation factors. (Page 74, column 1.) Plett teaches removing HSCs from the RWV and culturing them in methylcellulose media to differentiate them into various hematopoietic colonies; therefore, as required by claim 1, the HSCs' differentiation is suppressed to at least some degree. (Page 74, column 2.)

Plett does not teach first expanding stem cells in a culture container, then differentiating the same cells in the same container (one interpretation of claims 1 and 19, as well as claims 9, 10, and 27). Plett does not teach a multi-axis apparatus (claims 4, 22, and 28-30).

Goodwin teaches culturing first mesenchymal cells obtained from small intestine in the RWV, then adding epithelial cells to stimulate the mesenchymal cells to develop into organized epithelium. (Column 8, line 63, through column 9, line 4.) Goodwin teaches adding media to the RWV as the cells require. (Column 9, lines 10-11.)

Matthews teaches and claims methods of culturing HSCs in suspension and contacting them with differentiation factors, thereby differentiating the HSCs. (Example 2 at columns 49-53; claims 1, 2, and 6, e.g.) For example, Matthews teaches that

cultivation with Wnt-5a increases differentiation to the myeloid lineage. (Column 51, lines 8-11.)

Yugen Kaisha ECT teaches a culture apparatus containing a culture vessel inside an envelope that rotates around both an X-axis and a Y-axis. (See translation of detailed description, supplied by applicants, at paragraphs 24, 25, and 27; see also Figures 2 and 3.) Yugen Kaisha ECT teaches culturing cells within the rotating culture vessel. (Translation of detailed description, paragraph 16.) Yugen Kaisha ECT teaches that a cell cultured in the rotating culture vessel is "hardly influenced of gravity," i.e. it is cultured under microgravity conditions. (Translation of detailed description, paragraph 27.) Yugen Kaisha ECT teaches that the simultaneous two-axis rotation gives rise to a resultant force that provides circulation of culture medium. (Translation of detailed description, paragraph 27; Figure 4.)

A person of ordinary skill in the art would have had a reasonable expectation of success in first carrying out Plett's HSC expansion method followed by Matthews's differentiation method because Plett teaches that HSCs expanded in the RWV retain their ability to yield hematopoietic colonies. The skilled artisan would have further expected success in carrying out Matthews's differentiation in Plett's RWV because Goodwin teaches differentiating progenitor cells in a RWV. The skilled artisan would have been motivated to combine the methods of Plett and Matthews in the RWV of Plett and Goodwin in order to obtain differentiated cells.

The person of ordinary skill in the art would have had a further reasonable expectation of success in substituting the plural axis clinostat of Yugen Kaisha ECT for

the RWV of Plett and Goodwin because both of these apparatuses give rise to microgravity culture conditions. Therefore, the RWV and the apparatus of Yugen Kaisha ECT are functional equivalents for each other. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-1396, quoting *Sakraida v. AG Pro, Inc.,* 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1982) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to carry out first the HSC expansion method of Plett and then the HSC differentiation method of Matthews in a microgravity environment provided by the apparatus of Yugen Kaisha ECT because Goodwin teaches such sequential steps and because Yugen Kaisha ECT's apparatus, like that of Plett and Goodwin, provides a simulated microgravity culture environment.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-27 and 29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 15, and 16 of U.S. Patent No. 7,163,821. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the instant apparatus claims

completely encompass the scope of the ‘821 patent claims and are, therefore, anticipated by the ‘821 claims.

Instant claim 1 is interpreted as being drawn to an apparatus with means for cultivating cells and applying a force to said cells; instant claims 20-22 further characterize the force as gravitational and require rotation around at least two axes; instant claim 29 requires that the apparatus comprise two frames that rotate around each other on two axes with the culture container attached to the inner frame. Claims 9 and 15 of the ‘821 patent are drawn to an apparatus that rotates a culture vessel around “1 or more axes” (i.e., at least 2 axes), wherein the apparatus contains two rotating units with the culture container attached to the first unit. Instant claims 23-25 merely characterize the force inherently produced by a rotating apparatus. Instant claim 26 requires the addition of a differentiation inducing agent, as does claim 2 of the ‘821 patent.

Claims 1-10, 28, and 30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4 of U.S. Patent No. 7,112,441 in view of Plett et al. (2001, *In Vitro Cell and Developmental Biology – Animal* 37: 73-78; reference 1 on 5/7/10 IDS), Goodwin et al. (1996, U.S. Patent 5,496,722; reference A), and Matthews et al. (1998, U.S. Patent 5,851,984; reference B.

Claim 1 of the ‘722 patent is drawn to a method of growing cells comprising encapsulating (“sealing”) cells in a container, then rotating the container around greater than 1 axis (i.e., “2 or more axes”). Claim 4 of the '722 patent further describes the

rotating unit as having an inner and outer frame attached to each other by rotary joints (i.e., they are "rotatably supported").

The '722 patent claims require a continuous media flow, but the instant claims do not exclude such a feature and, therefore, completely encompass the scope of the narrower '722 claims. The '722 patent does not claim a method that first suppresses differentiation of the cells and then induces differentiation of the cells.

Plett teaches isolating CD34+ hematopoietic stem cells (HSCs) from bone marrow and culturing them in a rotating wall vessel (RWV), which simulates microgravity. (Page 74, column 1.) Plett teaches culturing the cells in media, then supplementing the media every 48 hours with growth and differentiation factors. (Page 74, column 1.) Plett teaches removing HSCs from the RWV and culturing them in methylcellulose media to differentiate them into various hematopoietic colonies; therefore, as required by claim 1, the HSCs' differentiation is suppressed to at least some degree. (Page 74, column 2.)

Goodwin teaches culturing first mesenchymal cells obtained from small intestine in the RWV, then adding epithelial cells to stimulate the mesenchymal cells to develop into organized epithelium. (Column 8, line 63, through column 9, line 4.) Goodwin teaches adding media to the RWV as the cells require. (Column 9, lines 10-11.)

Matthews teaches and claims methods of culturing HSCs in suspension and contacting them with differentiation factors, thereby differentiating the HSCs. (Example 2 at columns 49-53; claims 1, 2, and 6, e.g.) For example, Matthews teaches that

cultivation with Wnt-5a increases differentiation to the myeloid lineage. (Column 51, lines 8-11.)

A person of ordinary skill in the art would have had a reasonable expectation of success in carrying out first the expansion method of Plett and then the differentiation method of Matthews using the method of the '722 patent because the '722 apparatus provides a microgravity environment, and Plett and Goodwin teach that microgravity environments are suitable for both cell expansion and differentiation.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 1-10, 28, and 30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4 of U.S. Patent No. 7,291,500 in view of Plett et al. (2001, *In Vitro Cell and Developmental Biology – Animal* 37: 73-78; reference 1 on 5/7/10 IDS), Goodwin et al. (1996, U.S. Patent 5,496,722; reference A), and Matthews et al. (1998, U.S. Patent 5,851,984; reference B.

Claim 1 of the ‘500 patent is drawn to a method of growing cells comprising encapsulating (“sealing”) cells in a container, then rotating the container around greater than 1 axis (i.e., “2 or more axes”). Claim 3 of the '500 patent further describes the rotating unit as having an inner and outer frame attached to each other by rotary joints (i.e., they are “rotatably supported”).

The '500 patent claims require a continuous media flow, but the instant claims do not exclude such a feature and, therefore, completely encompass the scope of the

narrower '500 claims. The '500 patent does not claim a method that first suppresses differentiation of the cells and then induces differentiation of the cells.

Plett teaches isolating CD34+ hematopoietic stem cells (HSCs) from bone marrow and culturing them in a rotating wall vessel (RWV), which simulates microgravity. (Page 74, column 1.) Plett teaches culturing the cells in media, then supplementing the media every 48 hours with growth and differentiation factors. (Page 74, column 1.) Plett teaches removing HSCs from the RWV and culturing them in methylcellulose media to differentiate them into various hematopoietic colonies; therefore, as required by claim 1, the HSCs' differentiation is suppressed to at least some degree. (Page 74, column 2.)

Goodwin teaches culturing first mesenchymal cells obtained from small intestine in the RWV, then adding epithelial cells to stimulate the mesenchymal cells to develop into organized epithelium. (Column 8, line 63, through column 9, line 4.) Goodwin teaches adding media to the RWV as the cells require. (Column 9, lines 10-11.)

Matthews teaches and claims methods of culturing HSCs in suspension and contacting them with differentiation factors, thereby differentiating the HSCs. (Example 2 at columns 49-53; claims 1, 2, and 6, e.g.) For example, Matthews teaches that cultivation with Wnt-5a increases differentiation to the myeloid lineage. (Column 51, lines 8-11.)

A person of ordinary skill in the art would have had a reasonable expectation of success in carrying out first the expansion method of Plett and then the differentiation method of Matthews using the method of the '500 patent because the '500 apparatus

provides a microgravity environment, and Plett and Goodwin teach that microgravity environments are suitable for both cell expansion and differentiation.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action in order to assist the examiner with double patenting analysis in the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn, can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651